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## Central Cardiovascular Effects of *Alpha* Adrenergic Drugs: Differences between Catecholamines and Imidazolines

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### ABSTRACT

To check whether the central hypotensive effect of *alpha* adrenergic agonists is linked with the stimulation of *alpha*-2 receptors, such drugs were administered directly to the nucleus reticularis lateralis, which is an important site for the hypotensive action of clonidine. These experiments were carried out by microinjections (0.5  $\mu$ l on each side) in normotensive cats anesthetized with pentobarbital.  $\alpha$ -Methylnorepinephrine, a selective *alpha*-2 agonist (0.1–10  $\mu$ g/kg) had no hypotensive effect in this region, whereas potent *alpha*-1 agonists such as cirazoline (0.01–1  $\mu$ g/

kg) and ST 587 (1–10  $\mu$ g/kg), like clonidine, produced dose-dependent hypotensive effects. Our results suggest that *alpha*-2 selective catecholamines are not active in the nucleus reticularis lateralis region, whereas imidazolines induce a hypotensive effect whatever their affinity for one subtype of *alpha* adrenoceptors. Therefore, there may be some form of structure-activity relationship which would indicate the existence, in this particular region of the medulla oblongata, of sites preferring the imidazoline structure.

Based in particular on antagonism experiments with yohimbine and piperoxan, the central hypotensive effect of substances such as clonidine and  $\alpha$ -MNE is usually attributed to their selectivity for noradrenergic receptors of the *alpha*-2 subtype (for review see Schmitt, 1977; Berthelsen and Pettinger, 1977; Starke, 1981; Timmermans and Van Zwieten, 1982). Because  $\alpha$ -methylparatyrosine, reserpine, and 6-hydroxydopamine do not usually affect the hypotensive effect of clonidine and  $\alpha$ -MNE, these *alpha*-2 adrenoceptors are generally thought to be located postsynaptically (Finch, 1975; Kobinger and Pichler, 1976; Schmitt, 1977; Kobinger, 1978; Kubo and Misu, 1981). The hypothesis of a hypotensive effect linked with the stimulation of the *alpha*-2 adrenoceptors within the brain would imply that all selective *alpha*-2 agonists decrease the arterial blood pressure when administered directly to the action site of one of them, for instance that of clonidine.

Conversely, the agonists with opposite selectivity (maximum for *alpha*-1 adrenoceptors and minimum for *alpha*-2 adrenoceptors) might be expected not to have the same effects. To verify these hypotheses, we compared the effects of selective *alpha*-2 agonists such as  $\alpha$ -MNE with those of *alpha*-1 agonists such as cirazoline and ST 587. We choose  $\alpha$ -MNE because it is one among the most *alpha*-2 selective agonists in isolated organs as well in binding assays (Starke *et al.*, 1975; Langer, 1980; Rouot *et al.*, 1982). Starke *et al.*, (1975), for instance, reported that  $\alpha$ -MNE is the most potent agent in reducing the norepinephrine

release in the rabbit pulmonary artery. It is therefore considered as a highly selective agonist for presynaptic *alpha*-2 receptors.  $\alpha$ -MNE is also the most selective ligand for *alpha*-2 receptors in binding experiments performed on rat brain cortex (Rouot *et al.*, 1982). In these experiments, the *alpha*-2/*alpha*-1 selectivity was measured by the  $K_i$  ratio obtained by displacing [<sup>3</sup>H]yohimbine as a ligand for *alpha*-2 receptors and [<sup>3</sup>H]prazosin as a ligand for *alpha*-1 receptors; this ratio is 7.69 for  $\alpha$ -MNE. Conversely, cirazoline and ST 587 are proposed as the most potent *alpha*-1 agonists, especially because their pharmacological effects are mostly antagonized by prazosin, *e.g.*, their peripheral vasoconstrictive effects (De Jonge *et al.*, 1981; Cave *et al.*, 1981; Ruffolo and Waddell, 1982; Beckeringh *et al.*, 1982). In binding assays on cortical membranes, *alpha*-2/*alpha*-1 selectivity ratio (yohimbine sites/prazosin sites) is minimum for cirazoline and ST 587. This indicates that these compounds are the most selective *alpha*-1 agonists yet available (Rouot *et al.*, 1982; B. Rouot, personal communication).

It is also interesting to note that these *alpha*-adrenergic drugs belong to different chemical classes; catecholamines ( $\alpha$ -MNE and imidazolines (clonidine, cirazoline and ST 587; fig. 1). Therefore, the structure-activity relationship aspect will also be discussed in this report.

In order to compare the cardiovascular effects of these *alpha*-adrenoceptor agonists to those of clonidine as a reference substance, we performed microinjections of all these substances in the NRL, which we characterized as a site of action of clonidine (Bousquet and Guertzenstein, 1973; fig. 2). In fact, we previously reported that the electrolytic lesion of this me-

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ABBREVIATIONS: MNE, methylnorepinephrine; NRL, nucleus reticularis lateralis.

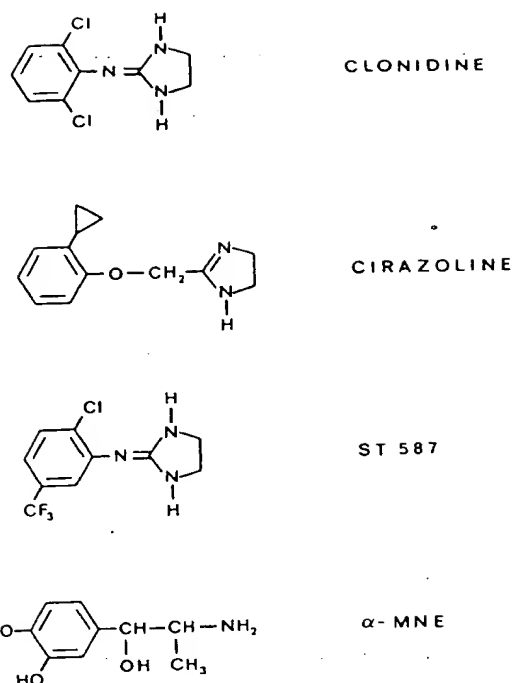


Fig. 1. Chemical structures of the  $\alpha$  adrenergic drugs injected into the NRL.

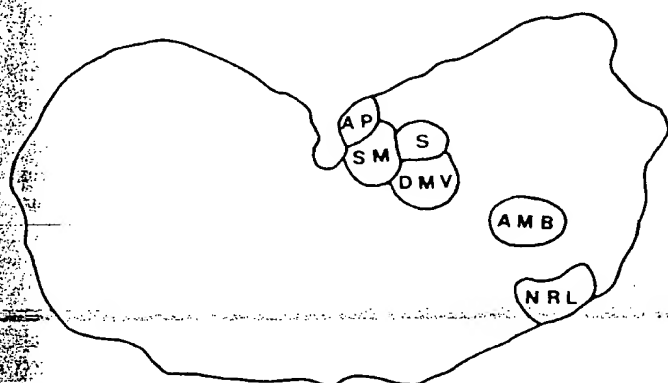


Fig. 2. Coronal section at the level of the obex of the brain stem of the cat passing through the medial part of the nucleus tractus solitarii (SM), the solitary tract (S), the dorsal motor nucleus of the vagus (DMV), the area postrema (AP), the nucleus ambiguus (AMB), and the nucleus reticularis lateralis (NRL) (Berman, 1968).

illary region completely prevents the hypotensive effect of clonidine injected i.v. (Bousquet *et al.*, 1975). We also showed that the region of the NRL is highly sensitive to this substance because doses as low as 75 ng/kg produce here a significant hypotension when the drug is applied with the microinjection technique (Bousquet *et al.*, 1981).

## Methods

Cats of either sex weighing 2 to 3.5 kg were anesthetized with pentobarbital (30 mg/kg i.p.). The animals were tracheotomized and artificially ventilated with a Bird Mark 8 ventilator. The animals were immobilized with pancuronium bromide (Pavulon) (2 mg/kg i.v.). The femoral artery and vein were cannulated for recording of systemic blood pressure and the injection of drugs, respectively. Blood pressure and heart rate were recorded with a Satham P23 Db transducer connected

to a Minipolygraph Gilson. The heart rate was monitored from the electrocardiogram with a cardi tachometer (IC-CT, Gilson Medical Electronics Inc., Middleton, WI).

**Microinjection in the NRL region.** Drug injections into the NRL were performed according to the method previously described by Bousquet *et al.*, (1980). The head of the animal was placed in a stereotaxic frame (La Précision Cinématographique Française, Ashières, France). To expose the dorsal surface of the medulla oblongata, the neck muscles were separated from the occipital protuberance and reclined downward. After removing the atlanto-occipital membrane the occipital bone was resected up to the protuberance and the dura mater was sectioned. At this stage, the two parallel glass needles (outer diameter, 150  $\mu$ m, 7 mm apart) were positioned level with the obex at an angle of 23° to the horizontal. The needle tips were then inserted 8 to 8.5 mm into the medulla oblongata. They were connected to Hamilton microsyringes (10  $\mu$ l) by means of polyethylene catheters. Slow injections (10 sec) were carried out by means of a micrometer.

Using the bilateral microinjection technique, we injected in the NRL very small volumes of drugs dissolved in 0.9% NaCl 0.5  $\mu$ l on each side. The stereotaxic insertion of the needles in the brain stem sometimes produced transient cardiovascular responses. In these cases, the microinjections were carried out only when arterial pressure and heart rate had returned to initial values.

At the end of each experiment, Evans blue was injected into the NRL under exactly the same conditions as the drug solution. Then the brain was removed and fixed in 10% formalin. Subsequent histological verification on 50  $\mu$ m frozen sections confirmed the desired location of needle tips and showed the diffusion of the stain around the point of injection.

**Drugs.** The following drugs were used in this study: 2-(2-chloro-5-trifluoromethyl-phenyl-imino)-imidazolidine nitrate (ST 587 NI, Boehringer Ingelheim Ltd., Elmsford, NY); 2-(2'-cyclopropyl phenoxy-methyl)-imidazoline HCl (LD 3098: cirazoline, Laboratoire d'Etudes et Recherches Synthelabo, Paris, France);  $\alpha$ -MNE (Hoechst, FRG); clonidine hydrochloride (Catapressan, Boehringer Ingelheim Ltd.); pentobarbital (Nembutal, Abbott Laboratories, North Chicago, IL); and pancuronium bromide (Pavulon, Organon Technica, France).

**Statistics and calculations.** Results are expressed as means  $\pm$  S.E.M. The statistical significance was calculated by Student's *t* test for paired comparisons.  $P < .05$  was set as the threshold of statistical significance.

## Results

**Effects of clonidine.** Clonidine, as the reference substance, was injected into the NRL of four normotensive, anesthetized cats. The total dose of 0.1  $\mu$ g/kg was injected bilaterally in a volume of 0.5  $\mu$ l. The mean blood pressure decreased from  $125 \pm 10$  to  $110 \pm 10$  mm Hg ( $P < .001$ ), i.e.,  $12.5 \pm 2\%$ .

This hypotension was accompanied by a bradycardia of  $10 \pm 2.5\%$  ( $P < .05$ ). The cardiovascular effects began within 1 min of injection, lasted more than 30 min and were reversible (fig. 3; table 1). A total dose of 1  $\mu$ g/kg produced a  $25 \pm 3\%$  fall in blood pressure ( $n = 4$ ; table 1). This effect was accompanied by a sustained bradycardia of  $26 \pm 7\%$ . The cardiovascular effect of this dose of clonidine also began within 1 min of injection but lasted more than 60 min.

**Effects of  $\alpha$ -MNE.** Bilateral microinjections of  $\alpha$ -MNE (0.5  $\mu$ l) were performed into the NRL of anesthetized cats.  $\alpha$ -MNE was administered at total doses of 0.1, 1 and 10  $\mu$ g/kg with four animals for each dose. Mean arterial pressures before the injections are given in table 1.

None of these doses of  $\alpha$ -MNE ever significantly affected either the mean arterial pressure or the heart rate after 30 min observation (fig. 3; table 1). At the doses of 1 and 10  $\mu$ g/kg, however,  $\alpha$ -MNE sometimes produced a weak depressor effect

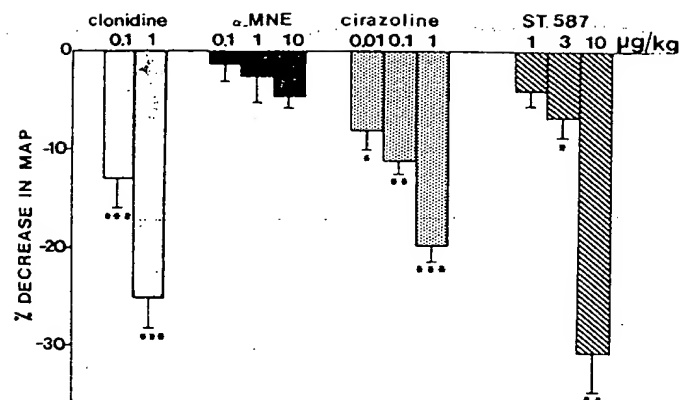


Fig. 3. Effects on the mean blood pressure (MAP) of various  $\alpha$  adrenergic drugs injected bilaterally in the NRL of anesthetized normotensive cats ( $n = 4$  for each dose). \*  $P < .05$ ; \*\*  $P < .01$ ; \*\*\*  $P < .001$ .

that was on the average less than  $5 \pm 1\%$ . No bradycardia occurred even when blood pressure slightly decreased.

**Effects of cirazoline.** Microinjections of cirazoline at total doses of 0.01, 0.1 and 1  $\mu\text{g/kg}$  were performed in anesthetized cats. Mean blood pressure and heart rate before injection, given in table 1, show that the initial values were similar in all series.

Cirazoline exhibited a dose-dependent hypotensive effect. Mean blood pressure decreased by  $8 \pm 2\%$  after a dose of 0.01  $\mu\text{g/kg}$ ,  $11 \pm 1\%$  after a dose of 0.1 and  $19.5 \pm 1\%$  after a dose of 1  $\mu\text{g/kg}$  (fig. 3; table 1).

This effect started within 1 min of injection. The duration of the effect depended on the dose; it lasted more than 30 min for the highest dose (1  $\mu\text{g/kg}$ ). This hypotensive effect was never accompanied by a significant change in heart rate. Nevertheless, we observed a weak bradycardia with the dose of 1  $\mu\text{g/kg}$ . Decrease in heart rate was less than 5%. Thus, cirazoline elicited a depressor effect when injected into the NRL which was similar to that observed with clonidine injected the same way.

**Effects of ST 587.** ST 587 was administered under the same conditions at doses of 1, 3 and 10  $\mu\text{g/kg}$ . We did not observe any significant hypotensive effect at the dose of 1  $\mu\text{g/kg}$ . However, at doses of 3 and 10  $\mu\text{g/kg}$ , ST 587 has hypotensive

effect, not accompanied by any heart rate modification, as shown in figure 3 and table 1.

At the dose of 3  $\mu\text{g/kg}$ , we observed a weak depressor effect with ST 587. Blood pressure fell by  $6.5 \pm 2\%$ . At the higher dose of 10  $\mu\text{g/kg}$ , blood pressure decreased immediately after injection ( $31 \pm 5\%$ ;  $P < .01$ ).

At this dosage, the peak effect was reached within 10 min of injection and lasted more than 1 hr and was reversible. Therefore, ST 587 produced cardiovascular effects which were similar to those obtained with cirazoline when injected into the NRL. This drug, however, was less potent than the former. In fact, 3  $\mu\text{g/kg}$  of ST 587 are needed in order to produce hypotensive effect similar to that obtained with 0.01  $\mu\text{g/kg}$  of cirazoline.

## Discussion

In an earlier study, we reported the high sensitivity of the NRL region to clonidine (Bousquet *et al.*, 1981). Microinjections of very low doses of clonidine at this level produce hypotension. The NRL is considered as a tonic vasopressive structure, a relay on the pathways of the baroreceptor reflex arc (Palkovits and Zaborszky, 1977). Here clonidine, as well as tetrodotoxin, inhibits an excitatory structure (Bousquet *et al.*, 1980). Other authors have, moreover, confirmed that a site for the central action of clonidine is located within the medullary lateral reticular formation. In fact, Sharma *et al.* (1978) and Cahusac and Hill (1983) reported an inhibitory effect of clonidine directly applied by means of microiontophoresis on excitatory cardiovascular neurons in the ventrolateral part of the brain stem. Chan and Koo (1978) and Wolf and Mohrland (1984) confirmed the existence of a ventromedullary site of action of clonidine in the rat. The microinjection of drugs into the NRL region was used as a means of analyzing the mechanism of hypotensive action of  $\alpha$  adrenergic drugs. We first used  $\alpha$ -MNE, a catecholamine shown to be one of the most selective  $\alpha$ -2 agonists (see the introductory section).  $\alpha$ -MNE is also of interest because it is reputedly the active metabolite of  $\alpha$ -methyldopa (for review see Porter *et al.*, 1977). We report here that it has no hypotensive effect at any dose applied into the NRL region. This observation complements our previous findings that norepinephrine itself had no effect there (Bloch *et al.*, 1973; Bousquet and Schwartz, 1983). Fur-

TABLE 1

Effects on the mean blood pressure (MAP) and heart rate (HR) of the  $\alpha$  adrenergic drugs microinjected into the NRL of normotensive anesthetized cats ( $n = 4$  for each dose)

Drug	Dose $\mu\text{g/kg}$	Before Injection		% Decrease After Injection	
		MAP mm Hg	HR beats/min	MAP mm Hg	HR beats/min
Clonidine	0.1	$125 \pm 10$	$155 \pm 9.5$	$12.5 \pm 2^{***}$	$10 \pm 2.5^*$
	1	$117 \pm 6$	$163 \pm 8$	$25 \pm 3^{***}$	$26 \pm 7^{***}$
$\alpha$ -MNE	0.1	$113 \pm 5$	$120 \pm 10$	$1.5 \pm 1.5$ (N.S.)	$2 \pm 1$ (N.S.)
	1	$117 \pm 4$	$120 \pm 5$	$2.5 \pm 2.5$ (N.S.)	$1.5 \pm 1.5$ (N.S.)
	10	$115 \pm 3$	$150 \pm 10$	$5 \pm 1$ (N.S.)	$3 \pm 3$ (N.S.)
Cirazoline	0.01	$136 \pm 9$	$158 \pm 7$	$8 \pm 2^*$	$1.5 \pm 1.5$ (N.S.)
	0.1	$128 \pm 9$	$147 \pm 12$	$11 \pm 1^{**}$	$2.5 \pm 2.5$ (N.S.)
	1	$119 \pm 13$	$135 \pm 13$	$20 \pm 1^{***}$	$4.5 \pm 4.5$ (N.S.)
ST 587	1	$113 \pm 12$	$140 \pm 10$	$4 \pm 1.5$ (N.S.)	$2 \pm 1.5$ (N.S.)
	3	$116 \pm 9$	$130 \pm 10$	$6.5 \pm 2^*$	$2 \pm 1.5$ (N.S.)
	10	$135 \pm 15$	$120 \pm 10$	$31 \pm 5^{**}$	$8 \pm 5$ (N.S.)

\*  $P < .05$ ; \*\*  $P < .01$ ; \*\*\*  $P < .001$

Moreover, this result shows that a selective  $\alpha$ -2 agonists do not necessarily induce hypotension when applied at the site of action of clonidine. We find a somewhat symmetrical situation within the medulla oblongata. In fact, according to Kubo and Misu (1981), De Jong and Nijkamp (1976) and Adberg and De Jong (1977),  $\alpha$ -MNE has a hypotensive effect when administered directly into the medial part of the nucleus solitarius, a dorsal medullary structure (fig. 2), where it stimulates a vasodepressive center, whereas clonidine in the same place has virtually no effect on arterial pressure. It is, therefore, impossible to relate the hypotensive effect of these compounds to a single action mechanism such as the stimulation of postsynaptic  $\alpha$ -2 adrenoceptors.

In another series of experiments, we observed that both imidazoline and ST 587, which have the lowest  $\alpha$ -2 adrenoceptor selectivity of the whole series of  $\alpha$ -adrenergic agonists, can produce dose-dependent hypotension, when administered into the region of the NRL, similar to that of clonidine. It appears, therefore, that the relative affinity of the imidazolines for the  $\alpha$ -2 adrenergic receptors does not influence their hypotensive effect. In fact, we report here that cirazoline is as active as clonidine when injected in the NRL region although its affinity for  $\alpha$ -2 adrenoceptors is one-tenth of that of clonidine (Rouot *et al.*, 1982).

Our results obviously only apply to the NRL inasmuch as cirazoline and ST 587 are known to have no hypotensive effect when administered systemically or in the vertebral artery (De Jonge *et al.*, 1981). The cardiovascular effects of a compound administered systemically or even into the whole brain may differ from those obtained when the substance is injected in a particular brain region for several reasons. A compound may act differently on several brain structures; thus, some drugs may have a hypotensive influence within the forebrain which may mask a vasodepressive action originating in the brain stem. This may occur with cirazoline and ST 587. Conversely, clonidine mainly depresses medullary structures, whereas it has a weak vasopressive influence within the forebrain (Bousquet and Guertzenstein, 1973; Trolin, 1975). One can also suggest that cirazoline and ST 587 might have important peripheral vasoconstrictive action which would mask their central hypotensive effects. Further experiments are needed to clarify these points.

We have observed that among the drugs we have tested so far, those containing an imidazoline ring (clonidine, cirazoline, ST 587) are hypotensive when administered directly into the NRL region, in contrast to the catecholamines ( $\alpha$ -MNE and norepinephrine) even when they have a selectivity for the  $\alpha$ -2 adrenoceptors ( $\alpha$ -MNE). There are parallels here with the observations of Ruffolo on the peripheral  $\alpha$  receptors. On the basis of structure-activity relationship, Ruffolo showed that the catecholamine-sensitive sites have different structural requirements than those for the imidazolines in smooth muscle (Ruffolo *et al.*, 1980, 1982, 1983; Ruffolo and Waddell, 1982). For instance, in the guinea-pig aorta and the field-stimulated guinea-pig ileum, the isomeric activity difference between the enantiomers of 2(3-4-trihydroxybenzyl) imidazoline is relatively small compared to that observed with phenylethylamines, suggesting that the stereochemical requirements made by peripheral  $\alpha$  adrenoceptors for imidazolines may be less than those for the catecholamines (Ruffolo *et al.*, 1983). The results confirm the authors' earlier observations which suggest that the imidazolines and the phenylethylamines interact differently

with the peripheral  $\alpha$  adrenoceptor. Similarly, Mottram and Thakar (1983) detected in the field-stimulated guinea-pig ileum such a difference in activity between clonidine and  $\alpha$ -MNE that the former could under certain conditions become an antagonist of the latter. On these models, the effects of stimulating these two types of sites are the same, namely contraction. Our results suggest that in the NRL region, there are imidazoline-preferring sites, the stimulation of which may inhibit a vasopressive structure. Contrary to what has been shown in the blood vessels, there do not seem to be any catecholamine-preferring sites with a cardiovascular function similar to that of the imidazoline-preferring sites in this medullary region.

In conclusion, we report here that, after injection into the NRL, an important site for the hypotensive action of clonidine,  $\alpha$ -MNE a selective  $\alpha$ -2 agonist, has no cardiovascular effect, whereas cirazoline and ST 587, like clonidine, have a hypotensive effect. These results confirm that the central mechanism of action of  $\alpha$ -MNE, postulated to be the active metabolite of  $\alpha$ -methyldopa, differs from that of clonidine. Not only are selective  $\alpha$  agonists inactive on the clonidine action site, but potent  $\alpha$ -1 agonists even have hypotensive effects there. Our results demonstrate that clonidine-like substances may stimulate imidazoline-preferring sites in the NRL region. These sites differ from the classical  $\alpha$ -2 adrenergic receptor because catecholamines with high  $\alpha$ -2 adrenergic affinity do not stimulate these receptors and also the affinity for the  $\alpha$ -2 adrenoceptors of imidazolines does not influence their effects. However, the nature of these receptors remains unclear.

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